

NEEDLELESS SYRINGE

FIELD OF THE INVENTION

The present invention relates generally to a needleless syringe device for
5 accelerating particles for delivery into target tissue of a subject.

The ability to deliver pharmaceuticals through skin surfaces (transdermal
delivery) provides many advantages over oral or parenteral delivery techniques. In
particular, transdermal delivery provides a safe, convenient and non-invasive
alternative to traditional drug administration systems, conveniently avoiding the
10 major problems associated with oral delivery (e.g. variable rates of absorption and
metabolism, gastrointestinal irritation and/or bitter or unpleasant drug tastes) or
parenteral delivery (e.g. needle pain, the risk of introducing infection to treated
individuals, the risk of contamination or infection of health care workers caused by
accidental needle-sticks and the disposal of used needles). In addition, transdermal
15 delivery affords a high degree of control over blood concentrations of administered
pharmaceuticals.

BACKGROUND TO THE INVENTION

Recently, a novel transdermal drug delivery system that entails the use of a
20 needleless syringe to fire powders (i.e. solid drug-containing particles) in controlled
doses into and through intact skin has been described. In particular, US Patent No.
5,630,796 to Bellhouse et al. describes a needleless syringe that delivers
pharmaceutical particles entrained in a supersonic gas flow. The needleless syringe
can be used for transdermal delivery of powdered therapeutic compounds and
25 compositions (e.g. drugs, vaccines, etc.), for delivery of genetic material into living
cells (e.g. gene therapy) and for the delivery of biopharmaceuticals to skin, muscle,
blood or lymph. The needleless syringe can also be used in conjunction with surgery
to deliver particles to organ surfaces, solid tumours and/or to surgical cavities (e.g.
tumour beds or cavities after tumour resection). In theory, practically any
30 pharmaceutical agent that can be prepared in a substantially solid, particulate form
can be safely and easily delivered using such devices.

One needleless syringe described in Bellhouse et al. comprises an elongate
tubular over-expanded converging-diverging nozzle having a rupturable membrane

initially closing the passage through the nozzle and arranged substantially adjacent to the upstream end of the nozzle. Particles to be delivered are disposed adjacent to the rupturable membrane and are delivered using an energising means which applies a gaseous pressure to the upstream side of the membrane sufficient to rupture the
 5 membrane and produce a supersonic gas flow (containing the pharmaceutical particles) through the nozzle for delivery from the downstream end thereof.

Transdermal delivery using the needleless syringe described in Bellhouse et al. is carried out with particles having an approximate size that generally ranges from between 0.1 and 250 μm . For drug delivery, an optimal particle size is usually at
 10 least about 10 to 15 μm (the size of a typical cell). For gene delivery, an optimal particle size is generally substantially smaller than 10 μm . Particles larger than about 250 μm can also be delivered from the device, with the upper limitation being the point at which the size of the particles would cause untoward damage to the skin cells. The actual distance which the delivered particles will penetrate depends upon
 15 particle size (e.g. the nominal particle diameter assuming a roughly spherical particle geometry), particle density, the initial velocity at which the particle impacts the skin surface, and the density and kinematic viscosity of the skin. In this regard, optimal particle densities for use in needleless injection generally range between about 0.1 and 25 g/cm^3 , preferably between about 0.8 and 1.5 g/cm^3 , and injection velocities
 20 generally range between about 100 and 3000 m/sec . These particle size and density ranges are also appropriate to the present invention.

There are two distinct phases of gas flow that occur in the device. The first phase is associated with the shock waves produced upon rupturing of the membrane and is called "the starting process" (or "starting transient"). The second regime of
 25 flow occurs upstream of the shock and expansion waves associated with starting process and is called quasi-steady nozzle flow.

As discussed in Bellhouse et al, it was considered that the particle velocity depended upon the flow in the starting process. The starting process is generated by a sudden impulse change in pressure within the divergent nozzle, and in the
 30 Bellhouse et al device is initiated at the throat of the nozzle. This is shown by the space-time ($x-t$) diagram of Figure 1. This Figure shows the distance downstream (positive values of x) and upstream (negative values of x) of the nozzle exit plane (i.e. the distal end of the nozzle) along the abscissa and shows time on the ordinate. The

time starts when the device is actuated. After rupturing of the membrane (which is located at around $x=-50$) at $t=0$, a steep front of high pressure (a shock wave 11) sweeps downstream along the length of the nozzle. This is closely followed by the so-called "contact surface" 12.

5 The contact surface 12 is the boundary between the gases that were previously separated by the membrane. It is well acknowledged that the gases do not mix appreciably at this boundary so the effect is one of the driver gas (the gas upstream of the membrane before rupturing) "pushing" the driven gas (the gas downstream of the membrane before rupturing) out of the nozzle like a piston, with
10 the contact surface 12 being analogous to the face of the piston. The contact surface 12 is closely followed by a secondary shock wave 13. The secondary shock wave 13 is followed by a series of oblique shock fronts 16 within a starting process (region 1 in Figure 1) with large variations in gas density and velocity (and therefore particle velocity). The starting process region 1 is substantially bounded by the shocks 11, 14
15 and 15; shock front 15 is mentioned further below.

 The starting process is followed by a regime of quasi-steady flow (in region 3). The quasi-steady flow is clean, that is to say substantially free of shock waves such that the velocity at a given point changes slowly enough with time to be accurately modelled by steady flow non time-varying equations. Quasi-steady flow
20 is thus different from truly steady flow in which the Mach number at a given point does not change over time, and unsteady flow in which the Mach number at a given point varies, and the flow is governed by unsteady equations. Both the starting process and quasi-steady flow are terminated by an oblique shock front 15 that is swept upstream of the nozzle exit, as a result of over-expanded nozzle operation.
25 This shock marks the boundary of region 2. As is mentioned in Bellhouse et al, it was thought that the particles, being initially positioned on, or very near to, the rupturable membrane, travelled with the contact surface 12 between the fronts of the primary and secondary shock waves 11,13. In the light of investigations by the present inventors, this view is now believed to be over-simplistic and (as is discussed
30 later) the gas-particle flow in such prior art devices is more complicated with groups of particles being accelerated by different mechanisms. It is still true that the starting process is critical to the acceleration of a proportion of the particles in prior art devices. In contrast to this, the essence of the present invention is based on the idea

of trying to avoid entraining the particles in the starting process.

Previous devices have utilised over-expanded nozzles which have an exit cross-sectional area A_e greater than the exit cross-sectional area of a correctly-expanded nozzle $A_{correct}$. Over-expanded operation occurs when the ratio P_{tot}/P_e of the total pressure P_{tot} to the ambient exit pressure P_e is insufficient for a correctly expanded supersonic flow for a given nozzle area ratio A_l/A_e (where A_l is the minimum diameter in the system). An overexpanded nozzle was used in prior art devices because, in order to obtain an adequate spread of payload on the target, it was thought that a large exit area was required. However, experiments have shown that using an over-expanded nozzle leads to flow non-uniformities such as oblique (or normal) quasi-stationary shock waves in the flow which serve to detach the flow from the nozzle walls. This flow accelerates the particles in a separated jet. Thus, surprisingly, it has been found that using a larger exit area does not necessarily increase the useful target area and in fact often causes the flow to detach resulting in a central jet core forming and a consequent low payload spread. This is undesirable and is known as "jetting".

Furthermore, devices of the prior art (such as those described in Bellhouse et al) utilise a convergent nozzle portion downstream of the particle-containing cassette. This portion acts as the interface between the relatively large membrane diameter and the relatively small nozzle throat diameter. The chosen throat diameter is controlled by the desired maximum choked mass flow rate through the device and the chosen membrane diameter is controlled by the need to be easily able to manufacture the cassette and hold the dose of particles required. Thus, upon actuation, the particles are forced through a constriction in the device. It is thought that this may increase particle-wall attrition and reduce the particle size and thereby undesirably affect the acceleration and penetration characteristics of the particles.

Experimental research sponsored by the present applicant has shown that the prior art devices produce two distinctive types of particle behaviour. Results from time resolved DGV (Doppler Global Velocimetry) measurements are shown in Figure 2, (see Kendall MAF, Quinlan NJ, Thorpe SJ, Ainsworth RW and Bellhouse BJ (1999), "The gas dynamics of a high speed needle-free drug delivery system", International Symposium on Shock Waves 22, Imperial College, London, July 19-23 and Quinlan NJ, Thorpe SJ and Ainsworth RW (1999), "Time-resolved Doppler

global velocimetry of gas-particle flows in transdermal powder drug delivery", 8th Int. Conf. On Laser Anemometry- Advances and Applications, 6-9 Sept, University of Rome, Italy. This shows a cross-section of the divergent portion of a nozzle 20 and gives the instantaneous speed of the particles at a time of 177 fs after rupture of the membrane (not shown).

As can be seen, the leading particles 21 are delivered in a wide cloud at a typical velocity of 200 - 400 m/s. A narrower quasi-steady stream of particles 22 follows the leading cloud at 650 - 800 m/s; it should be noted that the white circular image centred on the plane of the nozzle exit together with the dark shadow on its right hand boundary as drawn is an artefact produced by this measurement technique. The leading particles are associated with the transient starting process in the gas flow, while the high speed particles are entrained in the quasi-steady nozzle flow. As has been mentioned, the nozzle in this prior art device is over-expanded which means oblique shocks will be present in the nozzle. The detachment of the high velocity particle stream from the nozzle walls is a direct consequence of the shock induced separation of the nozzle gas flow due to these shocks. Referring again to Figure 1, the gas flow has been broadly categorised into three flow regimes:

- i) The Starting Process (region 1)
- ii) Shock-Processed Flow (region 2)
- 20 iii) Quasi-Steady Supersonic Flow (region 3)

The particle trajectories 17 are also shown in Figure 1. As can be seen, a significant proportion of the particles are accelerated within the starting process but then decelerate as they reach the secondary shock wave 13 and contact surface 12. A cloud front 18 of particles is seen to decelerate as it leaves the nozzle, the nozzle exit being represented by $x=0$. These particles are those entrained with the initial 200 - 400 m/s cloud attached to the nozzle wall. By nature, the starting process creates a flow having large variations in axial gas velocity and density. These are thought to be the two most important parameters for particle acceleration. There are also large variations in gas velocity and density radially. This flow regime is therefore considered unsuitable for drug delivery if uniform velocities and distributions are required. Another fraction of particles do not reach the secondary shock 13 but are processed firstly by the oblique shocks 16 within the starting process (in region 1) and then the upstream moving oblique shock 15 which defines the separated flow

within region 2. The final component of the particle payload is accelerated within the quasi-steady flow (region 3, particle trajectories not shown in Figure), before being separated by the quasi-stationary shock front 14 (defined in region 2). This acceleration path leads to the highest particle velocity of 850 m/s confined to a
5 separated jet of approximately 9 mm diameter.

It seems, contrary to previous beliefs, that the starting process, rather than being the chief accelerator of the particles, actually acts as an impediment to high velocity particles. The particles which exit initially in a large cloud seem to act as a barrier to particles entrained in the subsequent quasi-steady flow resulting in lower
10 overall particle velocities, which can be undesirable.

SUMMARY OF THE INVENTION

The present invention arises from the idea that, if one can prevent the particles from being entrained in the starting process flow, then substantially all of
15 the particles will be entrained in the subsequent quasi-steady supersonic flow, resulting in higher and more uniform particle velocities. The present invention also alleviates the problem of "jetting" by using a substantially correctly expanded nozzle and the problem of particle attrition by dispensing with a convergence downstream of the membrane.

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Accordingly, the present invention includes a method of accelerating a dose of particles in a needleless injection device having a driver chamber and a duct section downstream of said driver chamber, the method comprising:

opening closure means located between said driver chamber and said duct
25 section;

producing a primary shock wave travelling in a downstream direction in said duct section;

establishing a substantially quasi-steady flow of fluid in said duct section upstream of said primary shock wave; and

30 entraining and accelerating substantially all the dose of particles in said substantially quasi-steady flow for the duration of time that said particles are in said duct section.

In accordance with preferred embodiments of the method, a starting process

A further closure means may be provided and this or the first said closure means may comprise a rupturable membrane. When two closure means are used, the particles are advantageously positioned between them and each closure may have the same or different opening pressures.

5 A further aspect of the invention provides a particle retention assembly of or for use in a needleless injection device; said assembly comprising:

first closure means arranged to open when the pressure across it is P_1 ; and

second closure means which, in use, is located upstream of said first closure means and which is arranged to open when the pressure across it is P_2 ;

10 wherein P_1 and P_2 are different.

In connection with this aspect, there is also provided a method of entraining a dose of particles in a gas flow in a needleless injection device, the method comprising:

opening an upstream closure means when the pressure difference thereacross
15 is P_2 to produce a cloud of gas;

entraining said particles in said cloud of gas; and

opening a downstream closure means when the downstream closure means is exposed to said cloud of gas and entrained particles and when the pressure difference across said downstream closure means is P_1 ;

20 wherein P_1 is different to P_2 .

The invention provides in a yet further aspect a particle retention assembly of or for use in a needleless injection device; said assembly comprising:

first closure means arranged to open when the pressure across it is P_1 ;

second closure means which, in use, is located upstream of said first closure
25 means and which is arranged to open when the pressure across it is P_2 ;

a transfer duct which fluidly connects a location upstream of said second closure means to a location between said first and second closure means.

Preferably, the transfer duct causes a jet to impinge on the space between the closure means so as to mix any particles located there. There may also be provided a
30 closure in the transfer duct itself which can be arranged to open before the second closure means. The transfer duct may be positioned in the second closure means and may be embodied as a small hole or score.

In connection with this aspect, there is provided a method of entraining a dose

of particles in a gas flow in a needleless injection device, the method comprising:
providing a duct having upstream and downstream closure means;
providing a transfer duct which is arranged to permit gas from upstream of
said upstream closure means to be introduced into the space between said upstream
5 closure means and said downstream closure means.

There is further provided in another aspect a particle retention assembly of or
for use in a needleless injection device; said assembly comprising:
first closure means arranged to open when the pressure across it is P_1 ;
second closure means which, in use, is located upstream of said first closure
10 means and which is arranged to open when the pressure across it is P_2 ;
wherein one of said first and second closure means are constituted by
rupturable membranes which are scored or indented so as to provide controlled
rupturing.

The scoring/indenting is preferably along radial lines of the membrane to
15 achieve optimum controlled rupturing.

Preferably, particles are positioned between the first and second closure
means. One or more transfer ducts (possibly with their own closure means) located
between the driver chamber and the volume of gas between the first and second
closure means, may be used to facilitate a more controlled and uniform entrainment
20 of particles and flow initiation.

BRIEF DESCRIPTION OF THE DRAWINGS

Embodiments of needleless syringe device in accordance with the present
invention will now be described, by way of example only, with reference to the
25 accompanying drawings in which:

Figure 1 shows schematically an $x-t$ diagram which describes the flow
regimes present in a prior art device similar to the ones described in Bellhouse et al;

Figure 2 shows a cross-sectional view of the nozzle and the instantaneous
axial velocity of particles exiting the above-mentioned prior art device after 177 μ s of
30 flow;

Figure 3 shows schematically an $x-t$ diagram which describes the flow
regimes present in a device according to a first embodiment of the present invention;

Figure 4 shows a schematic cross-sectional side elevation of a target surface

and an impingement region;

Figure 5 shows a needleless injection device according to a first embodiment of the present invention in schematic cross-sectional side elevation;

Figure 6 shows a part of a schematic $x-t$ diagram which describes the
5 behaviour of the starting process in a device according to a second embodiment of the present invention when the gas in region 2 is subsonic and in region 3 is supersonic;

Figure 7 shows a part of a schematic $x-t$ diagram which describes the behaviour of the starting process in a device according to a third embodiment of the
10 present invention when the gas in regions 2 and 3 is subsonic;

Figures 8a and 8b are schematic cross-sectional (before and after) side elevations of the membrane region of a duct section of a fourth embodiment of a needleless injection device and illustrate a further aspect of the invention wherein the duct section has an enlarged duct portion to keep a more constant cross-sectional area
15 after membrane bursting;

Figure 9 shows a fifth embodiment which is a modification to the Figure 5 embodiment wherein the driver chamber has a larger cross-sectional area than the duct section, only part of the device being shown;

Figures 10a, 10b and 10c are a sequence of schematic cross-sectional side
20 elevations of the membrane region of a sixth embodiment of a needleless injection device and show another aspect of the invention relating to the creation of a mixed gas-particle cloud between two closures in a driver chamber;

Figures 11a, 11b, 11c, 11d and 11e show a seventh embodiment which involves a similar sequence to Fig. 10 except the rupture pressures and timing of the
25 particle entrainment are different;

Figures 12a, 12b and 12c are a sequence of schematic cross-sectional side elevations of the membrane region of an eighth embodiment and show the use of a transfer duct and a separate rupturable membrane to create a mixed gas-particle cloud between two closures in the driver chamber; and

30 Figures 13a, 13b, and 13c are a sequence of schematic cross-sectional side elevations of the membrane region of a modification of the eighth embodiment in which the transfer duct is positioned in the upstream closure means.

DETAILED DESCRIPTION OF THE INVENTION

Embodiment 1

5 The first embodiment of the invention is an air powered, disposable device and is shown schematically in Figure 5. The device could, however, be reusable and/or powered by a fluid other than air, for example helium, nitrogen or a mixture of gases. The selection of gas can be used to tune the performance of the device. Different gases or gas mixtures provide different quasi-steady gas velocities in the
10 same device and so the target particle velocity can be closely controlled by an appropriate driver gas selection.

 The device comprises an elongate tubular driver chamber 51 attached to a cylindrical duct section (or shock tube) 52 of the same diameter as the driver chamber 51. In this embodiment, each tube has a 6mm diameter, but in general the
15 diameters can be different to one another and can be of any practical size.

 In this embodiment, the driver chamber 51 has a length L_D of 65 mm and the duct section 52 has a length L_I of 30 mm. Other lengths are possible, and in fact the determination of the lengths is thought to be important in influencing the performance of the device (see later).

20 At the interface between the driver chamber 51 and duct section 52 is a rupturable membrane 53. The membrane 53 is of the type disclosed in Bellhouse et al and typically ruptures with a pressure difference across it in a range from around 5 to 20 bar, preferably 10 to 15 bar. The rupture pressure is an important device parameter but other rupture pressures could also be used depending on the desired
25 results. Control of the rupture process can be important for mixing and flow uniformity and may be enhanced by the prior indentation or scoring of the membrane, preferably along radial lines along which the rupture will propagate. This provides for more symmetrical membrane opening which in turn can provide a more symmetrical particle distribution at the target plane.

30 The downstream end of the duct section 52 is provided with a contoured divergent nozzle 54 in this embodiment. The nozzle 54 has an area ratio A_e/A_I such that correctly expanded flow is established within it when the membrane 53 has ruptured and the driver chamber 51 discharges. In practice this ratio (A_e/A_I) could

The particles 58 to be accelerated are in this embodiment initially located in the driver chamber 51 in the region of the rupturable membrane 53. The particles 58 do not necessarily have to be initially located adjacent to the membrane 53. If they
30 are located anywhere in the driver chamber 51 initially, they will not be entrained in the starting transient and so the invention should still operate. Also, the particles 58 could be located adjacent to the downstream side of the membrane 53 and the device should still work.

The functioning of this device is shown schematically by the $x-t$ diagram in Figure 3, with $t=0$ corresponding to membrane rupture. When the reservoir valve 57 is opened, gas flows from the reservoir 55 to the driver chamber 51 via the bleed hole 56 until the membrane rupture pressure is reached in the driver chamber 51. Thus, upon rupturing of the membrane 53, a shock 31 is generated which travels down the duct section 52 in the downstream direction. After a characteristic shock formation distance, the shock 31 travels ahead of the contact surface 32 at a constant speed. The contact surface 32 follows closely behind the shock 31 and the particles 33 follow behind that. Three flow regions can be identified:

- 10 i) Quiescent gas ahead of the shock wave 31 (region 1)
- ii) Gas between the shock 31 and the contact surface 32 (region 2)
- iii) Gas between the contact surface 32 and the particles 33 (region 3)

The distance between the particles 33 and the contact surface 32 increases initially with time because of the slower acceleration of the particles compared with the gas. The function of the duct section 52 is to provide a distance over which the shock 31 and the contact surface 32 can form so that the separation between the shock 31 (which will initiate the starting process at the transition between the duct 52 and the divergent nozzle 54), i.e. the "Nozzle Start" position in Fig. 3, and the particles 33 increases. The instantaneous delay time t_D (the time between the starting process initiating and the particles reaching the divergence 54) is a function of the particle size and gas type, whereby larger and denser particles are delayed more.

Simultaneously to the above, a first $(u-a)$ expansion wave 34 moves at a constant velocity (initially the speed of sound in the gas, a) from the location of the ruptured membrane 53 in the upstream direction until it reaches the bleed hole 56. Here it is reflected back as a $(u+a)$ wave 36 in the downstream direction where it accelerates until it eventually exits through the nozzle 54. The gas velocity in the downstream direction is denoted by u and the local speed of sound in the gas is denoted by a . Further $(u-a)$ expansion waves are created and the result is unsteady expansion fan 30 shown in Figure 3.

As the shock 31 moves through the tube in region 2, it serves to process the quiescent gas in region 1 to be in region 2 and heats up the this gas it processes, increasing its temperature and density. This is the so-called "shock-heating" process.

When the shock 31 reaches the start of the divergent nozzle 54, the starting process is initiated and a second ($u-a$) wave 35 is produced at the transition between the constant area 52 and divergence 54. In the embodiment of Figure 3, the driver gas is such and the pressure is sufficiently high for the Mach number of the gas in both regions 2 and 3 to be greater than 1. This second ($u-a$) wave 35 travels relatively slowly along the nozzle 54 in the downstream direction and accelerates once the contact surface 32 has overtaken it. This occurs because the gas ahead of the contact surface 32 in region 2 has been shock-heated by the passing of the shock-wave and so has a higher temperature and speed of sound than the gas behind the contact surface 32 in region 3. The gas in region 3 has been cooled by the expansion wave 34. Thus, when the second ($u-a$) wave 35 is overtaken by the contact surface 32, it speeds up in the downstream direction because the value of a drops suddenly (whereas the value of the velocity, u , is matched across the contact surface 32). The shock heating and expansion cooling processes are therefore beneficial in containing and in accelerating the starting process out of the device.

The length L_I of the duct section 52 is chosen so that the bulk of the particle cloud 33 is accelerated in the diverging duct 54 by a quasi-steady supersonic flow. This can be achieved by ensuring that the secondary shock 38 precedes, and leaves the diverging duct ahead of, the particle cloud. Quasi-steady flow is a substantially steady flow and in particular in this application is a flow substantially free of shock waves. Expansion waves (such as ($u-a$) wave 35) may be present in this quasi-steady flow.

Further, the length L_I of the duct section 52 is also important for the reason that, the longer it is, the more the particles 33 are accelerated and approach the gas

velocity. The gas in region 3 has a uniform density and velocity so the particles 33 experience a uniform acceleration due to the difference between their velocity and that of the gas.

A long length L_I would theoretically lead to particle velocities close to the gas velocity. However, in practice, increasing the length L_I to beyond a certain point will give diminishing returns due to shock attenuation and the contact surface 32 moving closer to the shock wave 31 as a result of boundary layer growth at the duct walls. There is therefore an optimum duct length of L_I which also depends on the other parameters (such as the driver gas species and pressure), and other constraints 10 of the system.

The length L_D of the driver chamber 51 is chosen so that the particles 58 have passed out of the device before the reflected expansion wave 36 passes out of the device. In other words, the length is preferably chosen so that the reflected expansion wave 36 nominally does not overtake the bulk of particle cloud 33. This 15 length ideally needs to be longer if light gases are used in the driver chamber (e.g. helium) which have a higher speed of sound. Thus, the boundary in time between the point where the shock wave 38 arrives at the divergent nozzle exit (effectively terminating the starting process) and the point where the reflected first ($u-a$) wave 36 arrives at the nozzle exit delimit a regime of clean, quasi-steady flow. Substantially 20 all of the particles 58 are entrained in this regime of clean flow (otherwise termed as the particle "delivery window").

Upon actuation, the bleed hole 56 causes the driver chamber 51 to be filled gradually until the membrane rupture pressure is reached. The bleed hole 56 (which could be constituted by an orifice plate) serves to ensure that during the discharge 25 process, a negligible amount of gas is able to escape from the reservoir 55 into the driver chamber 51. The bleed hole 56 therefore effectively creates an end-wall condition and has the effect of de-coupling the reservoir 55 from the flow system. Thus, the static pressure P_{static} in the driver chamber 51 remains substantially constant throughout the time the particles are accelerated. In this embodiment, the 30 static pressure P_{static} in the driver chamber 51 is the membrane rupture pressure. The atmospheric (or ambient) exit pressure initially at the nozzle exit is denoted by P_e . The ratio P_3/P_e (P_3 is the static pressure in region 3) is matched via analytical equations to the ratio A_I/A_e to ensure a quasi-steady correctly expanded flow through

the nozzle section 54. Since the total pressure is constant, the nozzle 54 will be correctly expanded for the duration of the particle delivery window resulting in attached flow for substantially the whole actuation period. The flow is therefore clean and attached for the period in which particles 58 are entrained. The above
 5 description relates to a correctly expanded nozzle. However, the system is robust and experiments have shown that substantially clean and attached flow can also be obtained with an under-expanded nozzle or even a slightly overexpanded nozzle. A correctly expanded nozzle is preferred though.

The bleed hole 56 also makes the device easier to silence because it restricts
 10 gas flowrate from the reservoir 55.

Ensuring that the particles 58 are entrained in the quasi-steady flow is believed to provide a further advantage. When a flow impinges on a flat area 41 (in this case the skin or other tissue), an "impingement region" (see Figure 4) is set up. This region comprises a stagnation bubble 42 which serves to reduce the speed of the
 15 particles 58 as they approach the surface of the skin 41. Ideally, the nozzle exit is maintained at a predetermined distance from the target plane by a spacer (not shown in Figure 4). The quasi-steady flow expanded from region 3 within the divergent duct is a supersonic flow and it is slowed down in the impingement region by a shock wave 43. With the correctly expanded divergent nozzle, this supersonic flow forms a
 20 parallel jet at the exit and thus creates an essentially normal shock 43 in the impingement region. This controlled impingement region ensures that the drug particles 58 maintain uniform velocities from the jet centreline to the outer edges as they decelerate after passing through the shock and before impacting the skin or tissue target.

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Embodiment 2

In the above embodiment, the gas flow in both regions 2 and 3 is supersonic (i.e. it has a Mach number, $M > 1$). However it is to be noted that the device also
 30 works when the gas in region 2 has a Mach number of less than 1. In this case, the nature of the starting process is altered as is shown in Figure 6, where identical reference numerals correspond to similar features. Here, the $(u-a)$ wave 35 initially travels upstream (because u is now smaller than a). This $(u-a)$ wave 35 and

subsequent ($u-a$) waves 37 are reflected and transmitted at the contact surface 32 as ($u+a$) and ($u-a$) waves respectively (only the transmitted ($u-a$) waves are shown in Figure 6). The complex system of waves 37 coalesces to form again a secondary shock 38.

5 Therefore the net effect of $M < 1$ in region 2 is a shift in the time of arrival at the nozzle exit of the secondary shock 38 (which effectively terminates the starting process). This can be seen by comparing Figures 3 and 6 wherein shock 38 arrives later in Figure 6 than in Figure 3, giving a reduced value of t_f in Figure 6. This simply changes the duration of the delimited regime of clean flow (the delivery
10 window) between the arrival of the secondary shock 38 and the arrival of the first reflected ($u-a$) wave 36 (not shown in Figure 6).

Embodiment 3

15 A further possibility for device operation occurs when the flow in region 3 has a Mach number of less than 1.

If the driven gas is air and the driver duct 51 is initially provided with:

- air (or nitrogen, or other gases with comparatively high molecular weights) with a closure means breaking at a sufficiently low pressure, or;
 - 20 • a gas species other than air with a higher speed of sound than air;
- then it is possible for the flow in region 3 to have a Mach number of less than 1 (see Figure 7). In this third embodiment, the gas in region 3 will expand to Mach 1 via a second unsteady expansion fan 71 initiated at the start of the nozzle divergent section 54, provided that the driver total pressure is above a critical value. This expansion
25 fan 71 brings the gas to sonic velocity at the upstream end of the divergent section 54. This sonic gas then expands quasi-steadily as a supersonic flow in the divergent section, as described in the earlier two embodiments. Furthermore, the starting process described in the earlier embodiments is present here, with the details dependent upon whether the flow in region 2 is greater or less Mach 1. The flow in
30 region 2 is subsonic in Figure 7. Thus a delivery window of quasi-steady flow, substantially correctly expanded and uniform, is achieved within which the drug particle payload is nominally entrained.

Further, this construction makes the device less sensitive to variations in the
25 membrane opening area. It is to be noted that the driver chamber area A_0 is
preferably not less than the duct section area A_1 because this would result effectively
in a divergence at the membrane. This would create waves at the point where the
particles start and so might be unlikely to allow the starting transient to pass out of
the nozzle before the particles 58 are entrained in the gas flow.

5 Embodiment 6

Another possible aspect of the invention to enhance particle mixing will now be described. Figure 10a shows a device having two membranes(101,102). The particles 58 are initially located between the two membranes in the driver chamber

10 51. The membranes are constituted so as to have different rupturing pressures, the upstream membrane 101 having a lower rupturing pressure than the downstream membrane 102. As the driver chamber 51 is filled and the upstream rupturing pressure is reached, the first membrane 101 ruptures (see Figure 10b), during which a jet of gas 103 discharges into the volume where the particles 58 are retained. It is

15 thought that this jet 103 causes mixing of the gas and particles to create a gas-particle cloud that is quite uniform (see Figure 10c). Thus, when the downstream membrane 102 ruptures at a higher pressure, the particles 58 are already entrained in a cloud and a more uniform spread of particles is obtained. The delay time caused by the difference in rupturing pressure of the two membranes is sufficient to allow gas-

20 particle mixing and a cloud to form and thereby overcome possible effects of gravity or attraction between the particles which cause the particles to bunch together (e.g. at the lowest point in the device) before rupture of the downstream membrane 102. Beneficially, a distance (e.g. a distance greater than one membrane radius) should separate the two membranes to allow for a clean membrane rupture and good mixing.

25 As a further modification, the particles 58 could initially be located upstream of the upstream membrane 101. When the upstream membrane 101 ruptures, the gas flowing into the space between the membranes carries the particles 58 with it and mixing is thus effected to produce a cloud in the same way as described above.

30 Embodiment 7

A further possible particle entrainment approach will now be described with reference to Figures 11a to 11e. Once again, the particles 58 are initially located

Embodiment 8

As can be seen from Figure 12a, a transfer duct 121 is provided to create a gas channel linking the driver duct to the volume between two membranes 123 and 124. The transfer duct is itself provided with a membrane 122 which ideally has a bursting pressure lower than that of membrane 123.

The membrane 122 is not essential and may be dispensed with, especially if the transfer duct has a very small cross-sectional area so as to be effectively decoupled from the driver duct 51.

It is generally necessary for the transfer duct 121 to have a cross-sectional area smaller than the driver duct 51 to ensure that the driver gas does not completely

bypass membrane 123 by flowing completely down the transfer duct 121. Further, membrane 122 may have a bursting pressure slightly higher than, or the same as, membrane 123. In this case, the side jet provided by the transfer duct 121 will be provided shortly after or at the same time as the jet provided by the opening of
5 membrane 123.

One or more transfer ducts 121 may be provided in the device and one or some of these transfer ducts could be routed to provide side jets in volumes not initially housing particles.

A preferable modification of the above is shown in Figures 13a to 13c of the
10 accompanying drawings. In this modification, the transfer duct consists of a small aperture 134 in the upstream closure means 131. Thus, when a gaseous pressure is exposed to the upstream closure means 131, some gas 133 is routed through the small aperture 134 which acts as a transfer duct prior to membrane rupture. This causes a similar mixing effect to that provided by separate, tubular, transfer ducts.

15 The upstream membrane 131 has an aperture 134 having a size small enough to prevent any particles escaping. The aperture is preferably circular and centred on the upstream membrane 131. Alternatively, the transfer duct may be provided by a membrane which is scored so as to burst in two stages; a centrally scored part would firstly rupture to allow a jet of gas 133 to enter the volume between the two
20 membranes and then the rest of the membrane ruptures allowing a quasi-steady gas flow to be established.

The transfer duct 134 may ideally be provided by one or more pin-pricks in the membrane 131 or the central part of the membrane may be comprised of a series of leaf-like flaps which open when a gaseous pressure is applied thereto. Any means
25 which allows gas to enter the volume between the upstream and downstream membrane before the upstream membrane ruptures fully is suitable.

Although in the description above the closure means has taken the form of a rupturable membrane, any other suitable rapidly openable closure means could
30 alternatively be used, such as a non-membrane cassette.

The divergent nozzle 54 could have a simple profile or one that is contoured to ensures that the nozzle gas flow is uniform and free of oblique shocks. In this case, the parallel and uniform nozzle exit flow also sets up a nominally flat

impingement shock and a more uniform impingement region.

The invention will still operate satisfactorily if the divergent nozzle 54 is dispensed with completely. In such a case, the gas undergoes a rapid expansion at the downstream end of the duct section 52. This case is equivalent to an under-
 5 expanded nozzle operation with a starting process in the downstream free jet which is analogous to the above starting process. Thus, a starting process of sorts is created even in the absence of a divergent nozzle and the concept of the invention is still applicable to devices having no divergent nozzle.